

Hepatotoxicity Associated With Isoniazid Preventive Therapy

A 7-Year Survey From a Public Health Tuberculosis Clinic

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MORE THAN 30 YEARS AFTER ITS introduction,¹ isoniazid preventive therapy for latent tuberculosis (TB) infection is still a subject of debate, mainly because of continuing concerns about hepatotoxicity.²⁻⁵ There are, however, good reasons to reconsider the hepatotoxicity of isoniazid at this time, with the anticipation that the risk is less than believed. The base of evidence for isoniazid hepatotoxicity, including a level of risk in the range of 5 to 20 cases of hepatotoxicity expected per 1000 persons receiving treatment with a 1% to 10% case-fatality rate, is composed of studies done more than 20 years ago.⁶⁻⁹ However, the early studies included patients who received a diagnosis of isoniazid hepatotoxicity on the basis of modest elevations of serum transaminase enzymes. Such patients would probably not be classified as having hepatotoxicity in current studies.

Monitoring for the safety of isoniazid is now done in most patients by a clinical evaluation for symptoms of hepatotoxicity rather than by screening for liver enzyme elevations because of the knowledge that up to 10% to 20% of patients who receive isoniazid experience a transient and harmless increase in serum levels of hepatocellular enzymes.^{10,11} Thus, a current reappraisal of isoniazid hepatotoxicity could plausibly detect an apparent lower rate simply because criteria for the diagnosis have changed.

Context Isoniazid preventive therapy for latent tuberculosis (TB) infection has been debated because of the risk of hepatotoxicity. The frequency of hepatotoxicity was 0.5% to 2.0% in early studies but may have changed with new criteria for diagnosis and patient selection.

Objective To determine the rate of isoniazid hepatotoxicity in patients managed according to current guidelines and practice standards.

Design Prospective cohort study.

Setting A public health clinic operated by the TB control program of a city-county public health agency.

Patients A total of 11 141 consecutive patients who started a regimen of isoniazid preventive therapy for latent TB infection from January 1989 through December 1995.

Main Outcome Measures The rate of developing symptoms and signs of hepatotoxicity among all persons starting isoniazid preventive therapy, among all those completing therapy, and by age, sex, and race.

Results Eleven patients (0.10% of those starting, and 0.15% of those completing treatment) had hepatotoxic reactions to isoniazid during preventive treatment. The rate of hepatotoxicity in persons receiving preventive therapy increased with increasing age (χ^2 for linear trend = 5.22, $P = .02$) and there were trends toward increased rates in women (odds ratio [OR], 3.30; 95% confidence interval [CI], 0.87-12.45; $\chi^2 = 3.28$; $P = .07$) and in whites (OR, 2.60; 95% CI, 0.75-8.95; $\chi^2 = 3.08$; $P = .08$).

Conclusions The rate of isoniazid hepatotoxicity during clinically monitored preventive therapy was lower than has been reported previously. Clinicians should have greater confidence in the safety of isoniazid preventive therapy.

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In addition, the consistent finding from those early studies of an association of hepatotoxicity with increasing age⁶⁻⁹ led to the recommendation to limit isoniazid preventive therapy in older persons except for those with an extreme risk of reactivation of TB.¹² Two recent studies^{13,14} found that when persons receive isoniazid preventive therapy in accordance with those current guidelines, the risk of fatal hepatotoxicity is significantly lower than was recorded in previous studies.

Population-based studies of isoniazid hepatotoxicity¹⁵⁻¹⁷ have been called for to assist in answering the ongoing questions about the safety of isoniazid. Our study was undertaken to deter-

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mine the rate of clinically relevant hepatotoxicity in a diverse group of patients who received isoniazid preventive therapy at 1 public health TB clinic over an extended period. For comparison purposes, hepatotoxicity associated with multiple-drug therapy for active TB was determined simultaneously.

METHODS

From January 1989 through December 1995, a prospective evaluation of isoniazid hepatotoxicity in patients at the Seattle-King County Department of Public Health Tuberculosis Clinic was undertaken. Patients receiving isoniazid in single- and multiple-drug regimens were instructed initially and at monthly appointments for drug refill about the signs and symptoms of hepatotoxicity. At those appointments, interviews were conducted by members of the clinic's nursing staff following a standardized written protocol that was used throughout the study. According to the protocol, all drug therapy was to be stopped by the patient immediately if the signs and/or symptoms of hepatotoxicity appeared; any signs and/or symptoms were then to be reported by telephone to clinic staff. All suspected cases of hepatotoxicity uncovered through standardized interviews with nursing staff or reported by patients between interviews were referred to 1 of the 2 authors who supervised a clinical and laboratory evaluation as described below. Prior to January 1992, C.M.N. performed all evaluations; after that date, S.V.G. performed most evaluations in consultation with C.M.N.

Three criteria for isoniazid hepatotoxicity were used, all of which were evaluated in each patient referred with symptoms of hepatotoxicity, and all were required for a classification of isoniazid hepatotoxicity: (1) symptoms of hepatitis (the progressive onset of anorexia, nausea, vomiting, and jaundice); (2) laboratory evidence of hepatic dysfunction, defined as a serum level of aspartate aminotransferase (AST) elevated over the normal level by at least 5 times with or without elevation of serum bilirubin level; (3) resolution of the signs and symptoms of hepatotoxicity after withdrawal of isoniazid and a de-

cision not to resume isoniazid treatment after the episode of hepatotoxicity resolved. All patients with hepatotoxicity also had serological testing for hepatitis A, hepatitis B, and (since February 1991) hepatitis C, and a clinical evaluation and appropriate laboratory testing for other disease- and drug-related causes of hepatic dysfunction, to identify associated cofactors for hepatotoxicity.

Rates of hepatotoxicity were derived by comparing the number of cases of hepatotoxicity from the 1989 through 1995 register with the total number of patients who began treatment with isoniazid alone or in multiple-drug regimens during that time. The latter data were obtained from a computer-based administrative registry of clients, which has been maintained by the clinic since 1986. That database contains demographic information on clients, their TB classification, and the types of services that they received, including drug regimens, while attending the clinic.

Rates of hepatotoxicity were determined for persons beginning therapy, and also for the number who completed therapy with isoniazid in single- and multiple-drug regimens. Denominator data for persons completing therapy were adjusted from the original denominator figures based on the clinic's performance statistics during the period of study: for persons receiving preventive therapy, 64% of those who began treatment completed it; for patients receiving multiple-drug therapy, 84% completed therapy (data on file, Tuberculosis Control Program, Seattle-King County Department of Public Health).

Rates of hepatotoxicity due to isoniazid were also calculated for several subgroups of the cohort that received preventive therapy (males vs females; nonwhites vs whites; and patients aged 0-14 years vs those aged 15-34 years, 35-64 years, and ≥ 65 years). As completion rates of preventive therapy were not available for those subdivisions of the cohort, rates were expressed only as a function of numbers of persons starting treatment. Comparisons of rates were done by means of the χ^2 statistic, using

Epi Info, version 6.04A (Centers for Disease Control and Prevention, Atlanta, Ga). For the comparison of rates in the 4 age groups, the χ^2 test for linear trend was used. Finally, logistic regression odds ratios of hepatotoxicity were determined with sex, age group (0-34 years, 35-64 years, and ≥ 65 years), and race (white and nonwhite) included to simultaneously adjust for all 3 factors in the model (Statistical Package for the Social Sciences [SPSS], version 7.0, Chicago, Ill). Statistical significance of the multivariate model was measured by 95% confidence intervals, which were considered significant if exclusive of unity, and confirmed with score tests.

RESULTS

During the 7-year study period, 11 patients experienced hepatotoxic reactions while receiving isoniazid (TABLE 1). The median age was 34 years (range, 27-67 years). Eight (73%) were female. The median interval between initiation of treatment and diagnosis of hepatotoxicity was 9 weeks (range, 19 days to 5 months), but 10 (91%) of the 11 episodes of hepatotoxicity occurred within 3 months of starting therapy. All 11 patients had highly elevated serum levels of hepatocellular enzymes and 9 (82%) of the 11 patients were hyperbilirubinemic. Two patients were taking acetaminophen and 2 were taking ibuprofen at the time isoniazid hepatotoxicity was diagnosed. Only 1 patient (9.1%, case 6, Table 1) was hospitalized because of hepatotoxicity. All 11 patients with hepatotoxicity recovered without sequelae.

Fifteen persons experienced episodes of hepatotoxicity while receiving multiple-drug therapy for active TB. All 15 were receiving isoniazid and rifampin, 12 were receiving pyrazinamide, and 8 were receiving ethambutol. Nine (60%) were female; the age range was 15 to 78 years (median age, 41 years); the range of peak AST levels was 299 to 2250 U/L (median AST level, 825 U/L). Several patients had associated illnesses and cofactors for hepatotoxicity. Three had human immunodeficiency virus (HIV) infection; 2 had hepatitis B infection; and 1 patient was an active intravenous drug

user of heroin and cocaine. Two patients were receiving acetaminophen.

One patient among those receiving multiple-drug therapy died due to hepatotoxicity: a 24-year-old woman who experienced fulminant hepatitis B infection while receiving isoniazid, rifampin, and pyrazinamide therapy for active TB. Two patients who were receiving multiple antitubercular drugs experienced hepatic dysfunction due to other causes. A 31-year-old woman took an intentional acetaminophen overdose during the fifth month of treatment with isoniazid, rifampin, pyrazinamide, and streptomycin. A 21-year-old black man receiving isoniazid, rifampin, pyrazinamide, and ethambutol had hepatic dysfunction due to graft-versus-host disease following bone marrow transplantation.

To verify our case ascertainment, we reviewed data from the Comprehensive Hospital Abstract Reporting System (CHARS), which is maintained by the Washington State Office of Hospital and Patient Dis-

charge Services, Washington Department of Health. For the study period, we searched the CHARS database for all residents of King County who received hospital discharge codes for hepatitis (code 573) and who were encoded as receiving antibiotics in the categories that included isoniazid (E931.8) or rifampin (E930.6) or both. Five records were reclaimed, of which 3 could be identified as cases in the study cohort. The 2 patients who could not be identified were a 70-year-old man, hospitalized in 1991 with pulmonary TB, toxic hepatitis, and coded for antibiotics that included both isoniazid and rifampin, and a 32-year-old woman hospitalized in 1995 with toxic hepatitis and the code for antibiotics that included isoniazid.

During the 7-year study period, 11 141 patients started isoniazid preventive therapy and 1427 started treatment for active TB. The rates of hepatotoxicity among patients starting and those completing therapy for active TB were far greater than those in patients receiving

isoniazid preventive therapy (TABLE 2). When age, sex, and race/ethnicity were analyzed in a logistic regression model, hepatotoxicity was associated with increasing age, and there were trends toward increased rates in women and whites (TABLE 3).

COMMENT

Our study shows that with the use of current guidelines for selection of patients for treatment, and with the application of a monitoring process based on patient education and monthly clinical evaluations, clinically relevant hepatotoxicity associated with isoniazid preventive therapy occurred at a very low frequency. Only 11 episodes of hepatotoxicity were encountered among the 11 141 persons who started isoniazid treatment during the 7-year study period. Hospitalization was required for only 1 patient, and there were no fatalities.

Our finding of approximately 1 case of hepatotoxicity per 1000 persons starting preventive therapy (and just over 1 case per 1000 persons completing preventive therapy), with no fatalities, is considerably lower than the frequency of hepatotoxicity recorded in earlier studies. For example, in the widely quoted US Public Health Service study,⁶ 92 cases of probable hepatitis, with 8 fatalities, occurred among 13 838 persons receiving isoniazid chemoprophylaxis, an adjusted rate of 10.3 cases per 1000 treated patients. A meta-analysis that reviewed 6 studies of isoniazid preventive therapy published from 1965 through 1984¹⁸ reported a summary rate of clinical hepatitis of 0.6% (6 per 1000 patients), several times the rate of hepatotoxicity reported in our study.

There are at least 2 reasons to explain why we encountered a lower rate of isoniazid hepatotoxicity than was noted in earlier studies. First, we used current guidelines for isoniazid treatment prepared by the Centers for Disease Control and Prevention and the American Thoracic Society.¹² Those guidelines, which are based in part on data from the early studies indicating that the risk of hepatotoxicity increased with age, recommend excluding patients over the age of 35 years from isoniazid therapy,

Table 1. Hepatotoxicity Due to Isoniazid in Patients Receiving Preventive Treatment of Latent Tuberculosis Infection, Seattle-King County Health Department Tuberculosis Clinic, 1989-1995

Case No.	Sex	Race	Age, y	Date Treatment Started	Date of Hepatotoxicity	Peak AST, U/L/Bilirubin, μ mol/L (mg/dL)*	Other Drugs
1	Female	White	55	5/8/89	7/20/89	1035/73.5 (4.3)	...
2	Male	White	34	2/15/91	4/3/91	1030/78.6 (4.6)	...
3	Male	Asian	29	3/23/92	6/18/92	399/20.5 (1.2)	...
4	Female	Asian	40	6/14/93	11/9/93	303/10.2 (0.6)	Acetaminophen
5	Female	Asian	33	10/13/93	11/1/93	1023/97.5 (5.7)	...
6	Female	Asian	27	12/27/93	3/1/94	844/80.4 (4.7)	Ibuprofen
7	Female	White	57	3/17/94	4/14/94	456/8.5 (0.5)	...
8	Female	Black	28	3/29/94	6/20/94	1068/119.7 (7.0)	...
9	Female	White	59	8/12/94	10/2/94	1050/181.3 (10.6)	Acetaminophen
10	Female	Black	29	12/8/94	3/11/95	1160/63.3 (3.7)	...
11	Male	Asian	67	5/5/95	7/11/95	610/47.9 (2.8)	Ibuprofen

*AST indicates aspartate aminotransferase.

Table 2. Rate of Hepatotoxicity in Persons Receiving Isoniazid Preventive Therapy and Treatment for Active Tuberculosis, 1989-1995

	Cases of Hepatotoxicity, No.	Rate of Hepatotoxicity, %	
		Persons Starting Therapy	Persons Completing Therapy*
Isoniazid preventive therapy (n = 11 141)†	11	0.10‡	0.15‡
Treatment for active tuberculosis (n = 1427)†	15	1.05‡	1.25‡

*Denominators for rate determinations: 11 141 \times 0.64 and 1427 \times 0.84 (see "Methods" section).

†Number of persons starting therapy.

‡P<.001.

except in cases of extreme risk of progression of the latent infection to clinical disease. Thus, only 20% of patients who received isoniazid in the current study were aged 35 years and older, while 59% of patients in the US Public Health Study⁶ were in that age group.

Second, it is possible that the type of monitoring we used, designed to detect only clinically relevant hepatotoxicity, not asymptomatic elevations in serum transaminase enzyme levels, accounted for the lower rate of hepatotoxicity that we observed. Routine biochemical testing would probably have resulted in a greater finding of hepatic dysfunction. For example, 1 prospective study of risk factors for isoniazid-induced liver dysfunction reported that among 101 treated patients, the rate of liver dysfunction as measured biochemically was more than 6 times greater than the rate of clinical hepatitis.¹⁹ Had we routinely monitored AST levels during treatment in our patients, and had the rate of enzyme elevations been 6 times that of clinical hepatotoxicity, the net effect would have been an addition of 60 cases to the 10 that occurred and an increase in the rate of hepatotoxicity from approximately 1 per 1000 to approximately 6 per 1000 patients treated, a rate in the range of other studies.

Clinical monitoring for isoniazid hepatotoxicity is based on educating patients about the symptoms of hepatotoxicity and instructing them to stop treatment immediately if such symptoms occur and to report to the clinic for biochemical confirmation. Clinical monitoring, rather than routine biochemical monitoring, is used by many public health TB clinics, according to a recent survey by Leff and Leff.²⁰ This suggests a high level of confidence in the safety of isoniazid on the part of the medical sector that has the most experience with the drug. In view of this information, Leff and Leff²⁰ have called for the establishment of new recommendations for TB drug toxicity monitoring "that are congruent with established therapeutic/toxicity relationships."

It is also possible that our observed rate of hepatotoxicity was low because we missed cases that occurred in persons who received isoniazid but were lost to follow-up. Thirty-five percent of patients did not complete their courses of preventive therapy, and it is conceivable that a patient receiving isoniazid from our clinic became ill with hepatotoxicity, sought care for that illness elsewhere, and escaped our routine attempts at follow-up. To address that weakness in our study we reviewed the CHARS hospital discharge database

and uncovered only 1 patient hospitalized in King County during the 7-year study period who could possibly have been such a lost case. Thus, it seems unlikely that undetected cases of hepatotoxicity occurring after loss to follow-up accounted for the lower observed rate.

Even though the current study found that isoniazid hepatotoxicity occurred less frequently, there were consistencies between this and previous studies. We observed an increasing risk of hepatotoxicity associated with increasing age and verified its greater frequency in women than in men (Table 3), as have previous studies.^{6,7,17,21,22} The borderline association of isoniazid hepatotoxicity with white race was surprising, as previous studies have suggested an increased risk in black and Hispanic women.^{14,17,21,22} Those studies, however, were not population-based. Had only our cases of hepatotoxicity been evaluated, a similar pattern would have been observed, with a minority (4/11 [36%]) occurring in whites (Table 1). This indicates the importance of determining the total numbers of patients receiving treatment in assessing the risk of adverse drug effects. We must point out, however, that as our findings were based on a small number of cases of hepatotoxicity (n = 11), an increase or decrease of 1 or 2 diagnoses

Table 3. Sex-, Age-, and Race/Ethnicity-Specific Rates of Hepatotoxicity in Persons Receiving Isoniazid Preventive Therapy, 1989-1995

	Cases of Hepatotoxicity, No.	Rate of Hepatotoxicity (Cases per 1000 Persons Starting Therapy)	χ^2 (P Value)	Adjusted Odds Ratio (95% Confidence Interval)
Total cohort (N = 11 141)*	11	1.0
Sex				
Males (n = 6066)	3	0.5	3.28 (.07)	1.0 (Reference)
Females (n = 5075)	8	1.6		3.30 (0.87-12.45)
Patient age, y				
0-14 (n = 1468)	0	...	5.22 (.02)†	...
15-34 (n = 7449)	6	0.8		1.0 (Reference)
35-64 (n = 1865)	4	2.1		3.17 (0.94-10.70)
≥65 (n = 359)	1	2.8		3.62 (0.43-30.42)
Race/ethnicity				
White (n = 1856)	4	2.2	3.08 (.08)	2.60 (0.75-8.95)
Nonwhite (n = 9285)‡	7	0.8		1.0 (Reference)
Asian (n = 5968)	5	0.8
Black (n = 1732)	2	1.2
Hispanic (n = 1050)	0
Other (n = 535)	0

*Number of patients starting treatment.

† χ^2 for linear trend.

‡Number of Asian, black, Hispanic, and "other" patients combined.

of hepatotoxicity in any category may have led to different findings.

It now seems important to confirm that the risk of hepatotoxicity of isoniazid under current conditions of clinical public health practice is less than previously believed, and we urge further study, particularly by public health clinics, where most patients receive treatment. Precise toxicity data are key to the successful design of studies that apply decision analysis techniques to evaluate medical interventions and to assist in the development of health policy. Several such studies,^{2,23-25} which have strongly influenced national policy on isoniazid preventive therapy during the past 20 years, include probability estimates for hepatotoxicity, including fatal cases, that are considerably higher than those of current studies,^{13,14} including ours. As an example of the importance of these variables, Salpeter and colleagues²⁶ recently performed risk-benefit and cost-effectiveness analyses that concluded that isoniazid preventive therapy produces small reductions in mortality rates and health care costs even

for low-risk tuberculin reactors older than 35 years, using assumptions that included a low risk of fatal isoniazid hepatotoxicity drawn from the survey by Salpeter.¹³

Isoniazid has an importance far beyond its role in analytical studies. Preventive therapy for latent TB infection is one of the major strategies in the national plan to eliminate TB from the United States.²⁷ Among the estimated 25 million foreign-born persons residing in the United States,²⁸ approximately 1 in 3 who immigrated from areas of the world where TB is still highly endemic have latent TB infection as a consequence of exposure to TB prior to arrival in the United States. For such persons, who now constitute the fastest-rising pool of TB cases in the United States,^{28,29} preventive therapy is the only possible means to lower their 5% to 10% lifetime risk of active TB. Likewise, isoniazid preventive therapy also has been shown to reduce significantly the highly elevated risk of TB in persons coinfecting with HIV and latent TB,^{30,31} now

numbered at more than 4 million persons worldwide.

If TB in the United States continues to evolve as a disease that targets foreign-born persons and those with HIV infection, it is imperative from a disease control perspective to be able to use preventive therapy to its fullest advantage. Isoniazid's reputation as a hepatotoxin,⁵ a burden it has borne since its inception in the 1960s, has hampered considerably its potential role in the prevention and control of TB in the United States. Recent studies in HIV-infected persons give some hope that alternative regimens of preventive therapy containing rifampin and pyrazinamide might supplant isoniazid.³¹⁻³³ However, until better preventive therapy regimens are verified, we must take optimal advantage of currently available tools to control TB.³⁴ Based on current information that suggests that isoniazid is less toxic than was previously believed, it deserves to be used more widely for the prevention and control of TB in the United States.

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